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Synthesis of (1→6)-*C*-Oligogalactosides by Iterative Wittig Olefination

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Abstract

Carbon-linked β-D-(1→6)-di-, tri- and tetragalactopyranosides have been synthesized by an iterative Wittig olefination employing a galactosylmethylene phosphorane as building block.

Keywords: Carbohydrates; Phosphonium salts; Wittig reactions.

Carbohydrate mimics in which the interglycosidic oxygen atom has been replaced by a methylene group represent a class of glycosidase resistant compounds which can be used for studies of carbohydrate binding affinities to biomacromolecules [1] and cellular interactions [2,3], and for explorative work in drug discovery [4]. Following this concept, various *C*-disaccharides have been prepared by monosaccharide coupling or *de novo* synthesis of a sugar unit on an existing one [5-8]. Quite recently, it has been pointed out [8] that most methods are only suitable for the synthesis of a particular structure and therefore lack generality. *C*-Trisaccharide mimetics have been synthesized by building up a central sugar unit on suitable carbon tethers holding two monosaccharides [1,9-11]. No synthesis of higher carbon-linked oligosaccharides have been reported so far.

We have developed a general method for the synthesis of (1→6)-*C*-disaccharides which involves as a key process the Wittig coupling of formyl *C*-glycosides and glycopyranose 6-phosphoranes [12]. The scope of the method was demonstrated by the synthesis of ten disaccharides, eight of which featured the β-glycosidic linkage. Expanding on the concept of this work we have made the Wittig coupling approach iteratively repeatable and would like to describe here the synthesis of β-D-(1→6)-*C*-oligogalactosides up to the tetrameric stage. The study of this linear homologative method in solution phase is also preparatory for work on a solid support.

For a reiteratable protocol, the monosaccharide building block **3** carrying a methylenephosphonium group at C-1 and a differentially protected hydroxyl group at C-6

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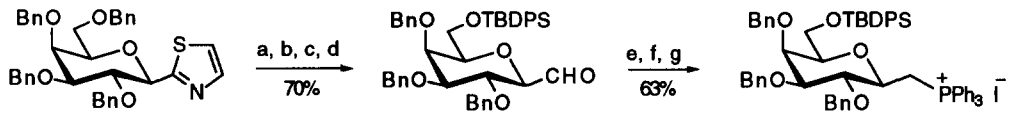
was designed to allow, in each cycle, the oligosaccharide assembly via Wittig coupling with a sugar aldehyde and the generation afterwards of the formyl group from the primary hydroxyl group. The galactopyranosylmethylene phosphonium salt[1] **3** was prepared in multigram scale starting from the known [13] thiazolyl *C*-galactoside **1**. The selective debenzylation and silylation followed by thiazole-to-formyl deblocking [14] afforded the formyl *C*-galactoside **2** which was converted into the phosphonium salt **3** by standard reactions. The aldehyde **2** would also be considered as a potential building block in an iterative Wittig olefination sequence with a sugar phosphorane. In the event, after deprotection, the primary hydroxyl group ought to be converted into a methylene phosphorane for the repetition of the cycle. This functional group transformation seemed to us more laborious than the conversion into the formyl group outlined above.



1 **2** **3**

Key: a, Ac_2O, AcOH, H_2SO_4, r. t.; b, MeONa, MeOH, r. t.; c, TBDPSiCl, pyridine, r. t.; d, TfOMe, CH_3CN, r. t.; then $NaBH_4$, MeOH, r. t. ; then $HgCl_2$, CH_3CN-H_2O, r. t.; e, $NaBH_4$, MeOH-Et_2O, r. t.; f, I_2, PPh_3, imidazole, 80 °C; g, PPh_3,120 °C.

Initial coupling of the ylide generated in situ from **3** (BuLi, THF-HMPA, -50 °C) with the readily available dialdogalactopyranoside **4** produced the alkene **5a** as a mixture of *E* and *Z* geometrical isomers in 1:9 ratio (J = 11.5 Hz) and 70% overall yield after column chromatography on silica gel. The preservation of the original configuration of the two sugar moieties was confirmed [12] by ^{1}H NMR analysis showing a $J_{8,9}$ value of 9.4 Hz (β-D-configuration) and $J_{4,5}$ value of 2.6 Hz (D-*galacto* configuration). Fluoride-induced liberation of the primary hydroxyl group in **5a** produced the alcohol **5b** whose oxidation with PCC proceeded smoothly and efficiently furnishing the aldehyde **6** (78%). Reiteration of this reaction sequence over two consecutive cycles extended the chain by two more sugar-alkene units. Unfortunately the desired alkenes[2] **7a** (36%) and **9a** (11%) were isolated in rather low yields. The major side products were sugar-alkenes (18 and 28% respectively) containing an additional double bond in a pyranose ring. Very likely these compounds are formed by the coupling of the ylide from **3** with enals arising from **6** and **8** by elimination of one molecule of benzyl alcohol. Hence it appeared worth examining the alternative way of chain growing by the use of the aldehyde **2** as building block. To this aim the alcohol **5b** was

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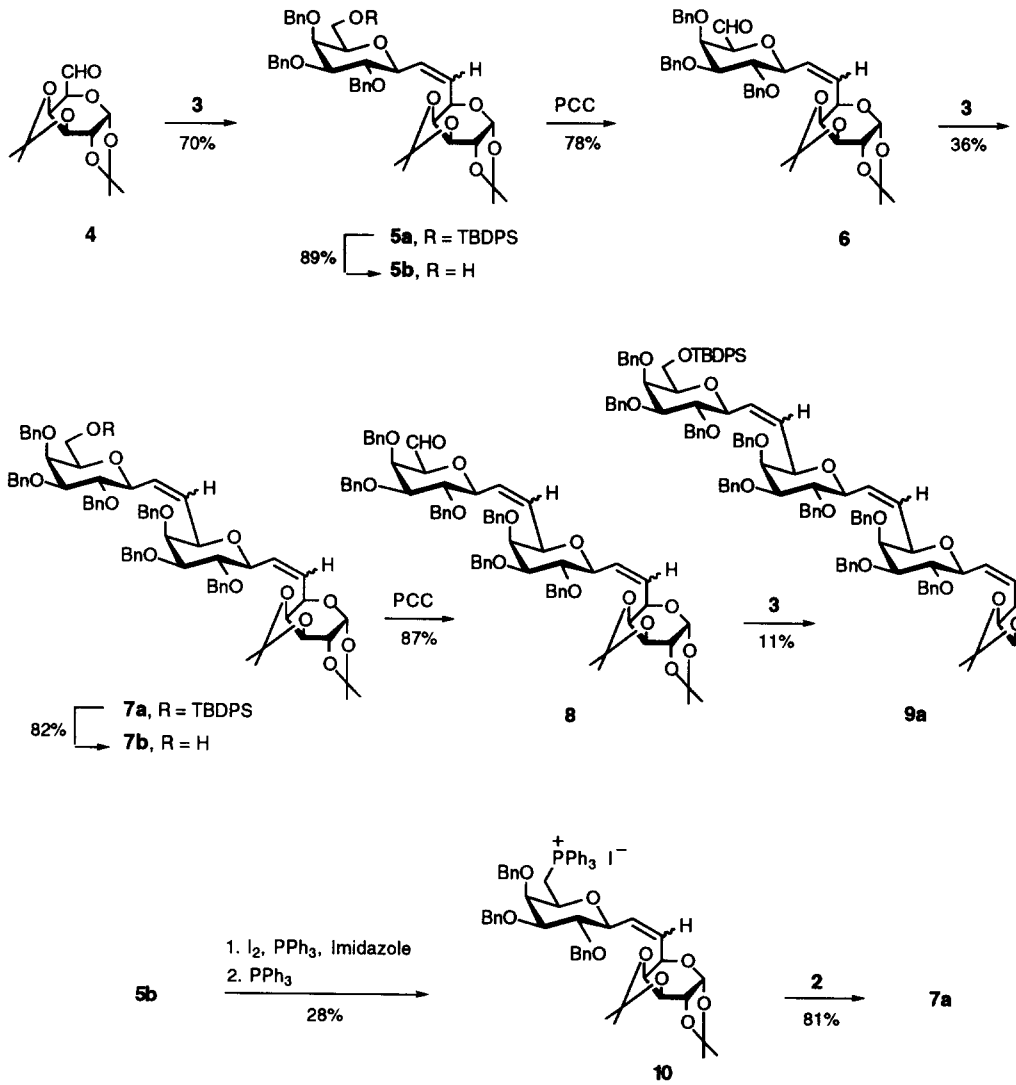
[1] **3**: mp 182-183 °C; $[\alpha]_D$ = -9.3 (*c* 0.8, $CHCl_3$). The β-D-glycosidic linkage was supported by a trans diaxal coupling constant value of 9.2 Hz.

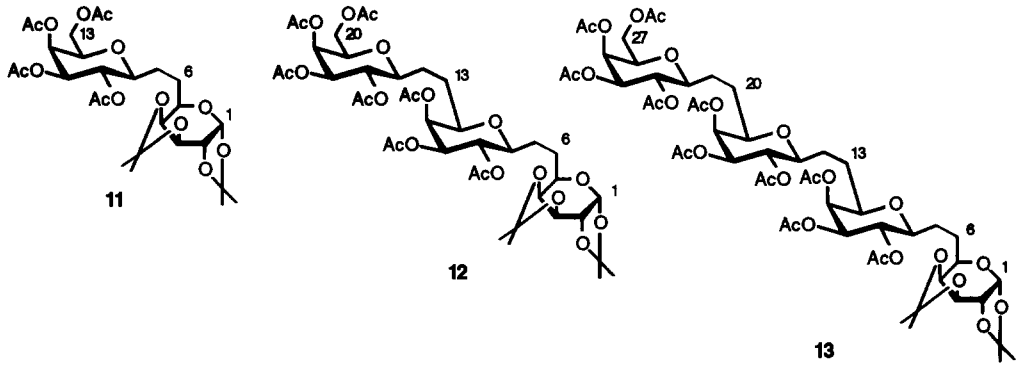
[2] The *E*/*Z* ratio for **7a** was ≥ 9:1 (J = 16.0 Hz) by ^{1}H NMR analysis. The configuration of the stereocenters adjacent to the newly formed double bond was supported by ^{1}H NMR data as described for **5a**. The *E*/*Z* ratio for **9a** could not be determined because of the complexity of ^{1}H NMR spectrum. The stereochemistry was assumed to be the same as that of its dimeric and trimeric conterparts.

converted into the phosphonium iodide **10** by iodination (I_2, PPh_3, imidazole) and reaction with PPh_3. The purification of the resulting sticky oil from the excess of PPh_3 was rather difficult so that **10** was isolated in low yield (28%). The coupling of the corresponding ylide with the formyl *C*-glycoside **2** afforded the alkene **7a** (*E*/*Z* < 1:9, J = 11.8 Hz) in a rewarding 81% yield. However, the overall yield of **7a** from **5b** in this cycle (23%) was slightly lower than in the other cycle (28%) employing the phosphonium salt **3** and the aldehyde **6**.



To complete the synthesis, isolated *E*/*Z* mixtures of alkenes **5b**, **7b**, and desilylated **9a**, were reduced by hydrogenation over $Pd(OH)_2$ on carbon. Since also the *O*-benzyl protective groups were removed in this single step, the resulting di-, tri-, and tetra-saccharides were

isolated and characterized as the corresponding *O*-acetyl derivatives[3] **11**, **12**, and **13**.



In conclusion, compounds **2** and **3** carrying highly reactive functionalities at the anomeric carbon with the desired stereochemistry already in place, appeared to be useful building blocks for a linear synthesis of *C*-oligogalactosides. These reagents eliminate the problem of the stereochemical control at the anomeric center that is often a crucial aspect in *C*-glycosidation reactions. Similar building blocks with the *gluco* and *manno* configuration should be equally accessible and then employed for the assembly of the corresponding (1→6)-*C*-oligosaccharides. In these cases, the elimination reaction observed in the above *galacto* series should be less pronounced.

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[3] **11**: $[\alpha]_D$ = -32 (*c* 1.9, $CHCl_3$). **12**: $[\alpha]_D$ = -20 (*c* 0.6, $CHCl_3$); MALDI-TOF MS: 898.2 ($M + Na^+$), 914.6 ($M + K^+$). **13**: $[\alpha]_D$ = -12 (*c* 0.2, $CHCl_3$); MALDI-TOF MS: 1184.8 ($M + Na^+$), 1201.3 ($M + K^+$).